UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,765	11/28/2000	Dale B. Schenk	15270J-004771US	6821

20350 7590 01/25/2006

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/723,765
Filing Date: November 28, 2000
Appellant(s): SCHENK, DALE B.

Joe Liebeshuetz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11-10-05 appealing from the Office action mailed 5-4-05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. The after final amendment submitted with the brief has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

Obviousness type double patenting over US Application No. 09/979,701 as now moot see 7.1.1 of the Brief.

Obviousness rejection under 35 USC 103(a) as the Petition for inventorship change submitted 5-7-04 is granted and thus Schenk WO99/27944 is disqualified as prior art.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Kayed et al., J. of Mol. Biol., 287(4):781-96, 1999

Schenk et al., Nature, 400:173-77, 1999

Games et al., Nature 373(6514):523-7, 1995

Chen et al., Progress in Br. Res., 117:327-34, 1998

Masliah et al., Neuroscience 16(18):5795-811, Sept. 15 1996

Irizarry et al., Neuroscience 17(18):7053-59, Sept. 15, 1997

Munch et al., J. Neural Transmission, 109(7-8):1081-87, July 2002

Lemere et al., Society for Neuroscience Abstracts, vol. 25, part I, Abstract 519.6, 29th Annual Meeting 10/23-10/28, 1999

Schenk, Nature, 400:173-177, 1999

McMichael, US 5,753,624, May 19, 1998

Kline, US 5,851,996, Dec. 22, 1998

Findeis, US 5,854,215, Dec. 29, 1998

Findeis, US 5,854,204, Dec. 29, 1998

Schenk, WO99/27944, June 10, 1999

Skolnick et al., Trends in Biotech., 18(1):34-39, 2000

Jobling et al, Mol. Microbiol., 5(7):1755-67, 1991

Check et al., Nature 422:370-372, 2003

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and In re Goodman, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 36 and 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 59-104 of Application No. 09/724,940. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '940 claims. Both instant claims and the '940 claims are drawn to methods of prophylaxis or treating Alzheimer's (patients inherently at genetic risk for disease) via administration of immunogenic fragments of beta amyloid, in particular where the fragments are designated as residues 1-7, see claim 66 and 89 of the '940 application. The fragments are linked to carrier molecules to form conjugates and for patients with genetic risk. A D-amino acid while not the natural peptide form is sufficient to stimulate antibodies and constitutes carrier where present at residues 8, 9, 10, or 11 and where further comprising conjugate portions Thus, the administration is to a species or sub-genus of the same peptides as instant claims ant therefore renders instant claims obvious. Both applications are reciting administration of the peptides comprising an N-terminal segment of Abeta, the segment beginning at residue 1 of Abeta and ending at residues 7 of Abeta.

Claims 1, 14, 36, and 40-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 58, 65, 76, 78, 83, 88, 90, 99, 101, 106, 111, 113, 118 and 119 of allowed copending Application No. 09/724,567. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by,

or would have been obvious over the '567 claims. Instant claims recite administration of peptides comprising an N-terminal segment of Abeta, the segment beginning at residue 1 of Abeta and ending at residues 7-11 of Abeta. Similarly the '953 claims recite administration of A□ peptide residues 1-7 and 1-10 as specifically recited in claims 76, 78, 99 and 101. Accordingly, the '567 claims are directed to treating or prophylaxis with a particular species or sub-genus of Abeta peptides, residues 1-7 and 1-10 while instant claims are to the larger genus of peptides comprising an N-terminal segment of Abeta from 1 to 7-11. Allowance of the subgenus or species of 1-7 and 1-10 anticipates or render obvious the larger genus or sub-genus of N-terminal segments of 1 to 7-11 as instantly claimed. This rejection is necessitated by amendment in both instant and '567 applications as well as allowance of the amended '567 claims.

Claims 1, 14, 36, and 40-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 11, 59, 76, 88, 99, 106, and 111 of allowed copending Application No. 09/724,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '953 claims. Instant claims recite administration of peptides comprising an N-terminal segment of Abeta, the segment beginning at residue 1 of Abeta and ending at residues 7-11 of Abeta. Similarly the '953 claims recite administration of Abeta peptide residues 1-7. Accordingly, the '953 claims are directed to treatment or prophylaxis with a particular species or sub-genus of peptide Abeta peptides, while instant claims are to

the larger genus of peptides comprising an N-terminal segment of Abeta from 1 to 7-11. Allowance of the subgenus or species of 1-7 anticipates or render obvious the larger genus or sub-genus of 1 to 7-11 as instantly claimed. This rejection is necessitated by amendment in both instant and '953 applications as well as allowance of the amended '953 claims.

Claim Rejections - 35 USC § 112, 1st Paragraph

Claims 1, 14, 36 and 40-42 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing beta-amyloid plaque burden in cortical regions of PDAPP transgenic mice which over-express amyloid by administration of AN1792 (human Abeta1-42), rodent Abeta1-42 , Abeta1-5 conjugated to sheep anti-mouse IgG, and Aβ1-7 in tetrameric MAP configuration as exemplified and disclosed for example at pp. 62-64 and 100 of the specification, does not reasonably provide enablement for prophylaxis or treating any disease associated with amyloid deposits of Abeta in the brain of a patient, particularly in a human patient or for preventing or treating such diseases with the breadth of peptides claimed comprising an N-terminal segment of Abeta, the segment beginning at residue 1 of Abeta and ending at residues 7-11 of Abeta as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of

working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The claims are drawn to a method for treating or prophylaxis of disease associated with amyloid deposits of Abeta in the brain of a patient. Such diseases include Down's syndrome, cognitive impairment and Alzheimer's as noted via applicant's claims. Other amyloid associated diseases include prion disease, type II diabetes and pancreatic amyloidosis. Such diseases differ in etiology, pathology and effects. For example, Down's syndrome is caused via trisomy, type II diabetes via insulin dysregulation and/or non-responsiveness and prion disease via prion protein, see in particular Kayed et al., J. of Mol. Biol., 287(4):781-96, 1999. Further cognitive impairment may be induced via a host of genetic and environmental cues ranging from trauma to retardation as noted in Down's syndrome or trisomy individuals. Yet the instant model system is based on a gene mutation observed in individuals predisposed to Alzheimer's disease. The PDAPP model is not based upon and fails to address the etiology or pathology of alternative amyloid deposition diseases in brain other than Alzheimer's plaque deposition. Thus the PDAPP model is not recognized as being of commensurate scope for, or useful in, predicting treatments for diseases other than Alzheimer's disease.

The specification teaches that the administration of particular polypeptides is able to reduce beta-amyloid levels within the brains of mice which are transgenic for PDAPP. These mice exhibit Alzheimer's type over production and build up of beta-amyloid within the brain. However, as recognized in the art, these mice do not exhibit Alzheimer's

disease as in humans or plaque morphology and components which are the same as in humans, Alzheimer's disease, Down's Syndrome or other amyloidogenic diseases which are particularly known to be associated with paired helical filaments, neurofibrillary tangles and neuronal cell death, see in particular Schenk et al., Nature, 400:173-77, 1999 (IDS), Games et al., Nature 373(6514):523-7, 1995 (IDS), Chen et al., Progress in Br. Res., 117:327-34, 1998, Masliah et al., Neuroscience 16(18):5795-811, 1996 Sept. 15 and Irizarry et al., Neuroscience 17(18):7053-59, 1997 Sept. 15, 1997. Thus, the model system used is not recognized as providing for teachings that are predictive of the results that would be expected for the full scope of the claims, including for humans with paired helical filaments, neurofibrillary tangles and neuronal loss as in Alzheimer's disease. For example, the art recognizes that such processes are not represented in the in vivo models and therefore the model is not readily correlated to the human in vivo case with respect to these pathologies of Alzheimer's disease. Further, the art teaches a lack of correlation of beneficial effects shown in the mouse model system in humans and exhibit no relevant results with respect to the formation of paired helical filaments, see in particular Munch et al., J. Neural Transmission, 2002 July, 109(7-8):1081-87. Specifically, treatments that were effective in mice were shown to evoke neurotoxicity when practiced in humans. Thus, for the aforementioned reasons treatment of humans does not appear to be commensurate in scope with the claims.

Moreover, the model system does not fairly teach that the treatment is effective to prevent the onset of disease. As Applicant argues, Example 1 does exhibit that AN1792 (Abeta 1-42) can reduce the deposition of beta amyloid in the APP animals.

However, the Examiner notes that for all other treatments, the PDAPP mice exhibited amyloid plaques regardless of treatment regime. Moreover, the prevention of beta amyloid deposition fails to speak to the development of paired helical filaments, neurofibrillary tangles and neuronal loss associated with Alzheimer's disease in vivo. Even today, the art fails to recognize prevention of Alzheimer's disease. While the in vivo model is commensurate in scope with reducing or inhibiting amyloid plaque deposition, the recitations of the claims are not fairly provided.

The method is based upon findings which show particular strategies of targeting amyloid plaque removal via antigen administration. Evidence that such therapy can be effective in the removal of amyloid plaque burden is exhibited by Lemere et al., Society for Neuroscience Abstracts, vol. 25, part I, Abstract 519.6, 29th Annual Meeting 10/23-10/28, 1999 (IDS) using antigen Abeta1-40 and Schenk, Nature, 400:173-177, 1999 (IDS) using antigen Abeta1-42. Similarly, McMichael, Kline, Findeis and Schenk as set forth below teach effective treatment of Alzheimer's disease and cognition deficits associated with amyloid plaque deposits upon beta-amyloid administration or beta-amyloid 1-28 administration. However, what these references do not teach is the regions or epitopes within beta-amyloid1-42 or 1-28 peptide which are responsible for mediating plaque removal or the beneficial effects. In particular neither instant specification nor the art recognize treatment with the scope of peptides now claimed comprising an N-terminal segment.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of

single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response.

These concepts are exemplified within the specification. For example, the specification discloses experimentation using a group of human Abeta peptide sequences consisting of peptides of residues 1-5, 1-12, 13-28, and 33-42 conjugated to sheep anti-mouse IgG, see in particular pp. 62, lines 25-32. Yet only the conjugated fragment of Abeta1-5 was effective to reduce plaque burden in PDAPP mice, and only within the cortex, see in particular pp. 64, lines 30-31. Thus, the specification exemplifies the unpredictability and variability in the effectiveness of various peptide immunogen constructs in effecting amyloid plaque removal. Alzheimer's pathology is not limited to cortex, but also effects hippocampus and other regions of the brain that were not noted to be significantly decreased, see in particular p. 65, lines 1-3. Thus, the

specification does not enable the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke immune responses that would provide for these effects. The specification provides essentially no guidance as to which of the nearly infinite possible choices is likely to be successful and the skilled artisan would not expect functional conservation among homologous or variable sequences and cannot predict protective epitope structures without further undue experimentation.

The claims are directed to administration of an "effective dosage". The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 U.S.P.Q. 150,(CCPA 1977), which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph". In particular the "effective dosage" is to be administered to the patient so as to provide a method of treating a disease associated with amyloid deposits of Abeta in the brain of a patient. Yet the recitation fails to not the particular symptoms, pathology or effects so as to be alleviated or treated.

Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with

the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

While the artisan recognizes the PDAPP mouse as a model system providing similarities to Alzheimer's disease, the art reflects numerous differences in the pathology between that of the PDAPP mouse and that of human Alzheimer's patients. For example, note that PDAPP mice do not exhibit paired helical filaments, a hallmark of Alzheimer's pathology in humans. In addition, while the data presented in *in vivo* clinical trials is compelling, the trials differ in that the peptides administered were of AN1792 or full length beta-amyloid peptide of residues 1-42. Moreover, the trials appear to be inconclusive in findings as to prevention or treatment of Alzheimer's. For example, as noted in Check et al., IDS reference 349, p. 371, column 3, paragraphs 2-3, "it is impossible to prove that plaques were cleared" and similarly, "the authors should not conclude that clearance of the plaques is due to the treatment." Further, the trial is not commensurate with prevention or even prophylaxis, but to decreased cognitive

decline as noted in the declaration. This is in contrast to the broad scope of the claims with respect to the recitation of prevention with the peptides as instantly claimed. Moreover, applicant's basis for prevention within Example1 is only directed to the Abeta1-42 species and not to the full scope of the claims. There are no teachings within the PDAPP model with respect to paired helical filament formation in Alzheimer's. Thus, applicant's arguments and declaration fail to provide sufficient evidence that the model system is predictive of treatment or prophylaxis in the in vivo clinical situation in humans. Further, the teachings are not commensurate to the full scope of the claims, but instead are directed only to the AB1-42 species and to inhibiting or reducing amyloid aggregate plaques in brain.

The ability to make and test is not the standard for an enabling disclosure. The instant specification fails to establish the structure that is required for the claimed biological activity in prophylaxis or treatment of Alzheimer's disease, and the model system is not established as predictive for the testing of such effects via the multiple peptide constructs claimed. In the absence of guidance, a practitioner in the art of molecular neurobiology would have to resort to a substantial amount of experimental trial and error to produce a peptide of the claimed formula that also retains the biological activities recited in the claims. This trial and error would clearly constitute undue experimentation and, therefore, the instant specification is not enabling for the full scope of the peptides as claimed. The standard for an enabling disclosure is not one of making and testing and the claims constitute a "wish to know". There is only a single conjugate peptide amongst those claimed that is disclosed as exhibiting positive effects

in the model system and that is the Aβ1-7 peptide in MAP configuration as exemplified at pp. 99-100. As previously noted, the specification discloses experimentation using a group of human Abeta peptide sequences consisting peptides of 1-5, 1-12, 13-28, and 33-42 conjugated to sheep anti-mouse IgG, see in particular pp. 62, lines 25-32. Yet only the conjugated fragment of Abeta1-5 was effective to reduce plaque burden in PDAPP mice, and only within the cortex, see in particular pp. 64, lines 30-31. Thus, the specification exemplifies the unpredictability and variability in the effectiveness of various peptide immunogen constructs in effecting amyloid plaque removal. The claims are directed to a broader range of peptides. Yet no predictability is established for expecting similar function from these constructs when only a single member of the genus was effective and event then was only effective for lowering cortical Aβ levels as disclosed at p. 100, lines 23-26.

While applicants need not demonstrate that every peptide construct of the claims works, the disclosure of the specification must be commensurate in scope with what is claimed. The claims encompass peptides comprising an N-terminal segment of beta amyloid beginning at residues 1 of beta amyloid and ending at residues 7-11 of beta amyloid and the segment is linked to a carrier molecule to form a conjugate wherein the carrier molecule helps elicit an immune response to the N-terminal segment. However, this is not enabling because there is no reasonable expectation that any compound which structurally falls within the scope would more likely than not function in accordance with the manner described, i.e., to effect treatment and prophylaxis

consistent with the requirements for treatment or prophylaxis as contemplated to be sufficient to cure, eliminate or reduce the risk as encompassed at p. 36.

The instant specification fails to provide this information, and one cannot predict based upon the disclosure whether the activity will be possessed. Therefore, one cannot use the peptides without first making and testing them, which is not the standard for enablement. The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. Applicant's 'make and test' position is inconsistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen v. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8 USPQ2d, 1400 (CAFC 1988). In re Wands stated that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that the;

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to

achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."
pp. 12-13) in that the screening is not undue, the teachings are commensurate and not of extreme breadth.

The claims are now directed to "A method of treating a patient having Alzheimer's disease," and to "A method of prophylaxis of Alzheiemr's disease in a patient at risk of the disease". However, Alzheimer's disease is a human condition with multiple facets of recognized pathology and symptoms. While the specification teaches that peptide treatment may be effective to reduce plaque burden, this is the only noted benefit of treatment. Such is not correlated to other inwardly associated pathologies such as neurotoxicity, neurodegeneration, paired helical filament formation, cognitive deficit, cognitive decline or inflammation. In addition, reduction in plaque burden, while aimed at alleviating the presumptive primary cause of Alzheimer's disease, this cellular effect (reduction in plaque burden) is not evidenced to translate to any outward

treatment or benefit to Alzheimers patients in the form of alleviating any Alzheimer's symptoms such as dementia, deficits in learning and memory, irritability, anxiety, depression or sleep disturbances. While the results within the declaration of Dr. Koller are probative to a decline in functional deficits, it is also clearly noted that, "the change from baseline to week 64 DAD scores failed to reach statistical significance," and hence the studies data is not conclusory or evidential to decreased decline in treated patients, and as previously mentioned the administration protocol is not commensurate with the noted treatment of the claims. In particular, the peptide constructs differ in that the Koller administration is of full length beta amyloid. Moreover, the specification does not provide guidance for identification of the new subgenus of individuals deemed to be at risk of disease or that modulation of plaque burden is evidentiary to prophylaxis or prevention of disease. The recitation of, "an effective dosage to treat disease" or "an effective dosage to effect prophylaxis" is circular and does not guide the artisan to any testable or ascertainable effect whereby to determine that prophylaxis or treatment has occurred. The specification at p. 36 makes clear that both treatment and prophylaxis are intended to be in scope with "eliminate(ion) or reduced risk" as well as "sufficient to cure", see in particular lines 14-23. Yet even today, elimination of risk and cure are beyond scope. Moreover, the means for testing such absolution is not provided. Therefore the "effective dosages" remain indeterminate.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Claims 1, 14, 36, and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As in MPEP 2173.05, "The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954)." Here the phrase "an effective dosage" is indefinite in that the claims fail to state the function to be achieved. More than one effect is implied via the specification and/or relevant art. For example the treating may require antibody production, amyloid plaque clearance, enhanced performance in cognitive function or other such symptom of a disease associated with amyloid deposist of Abeta in the brain of a patient and/or Alzheimer's or risk of Alzheiemr's disease. The recitation fails to note the particular effects to be achieved such that the disease is "treated" or "prophylaxis" is provided. The claim lacks clarification as to the amount or suitable effect. As formerly of discussion Alzheimer's is a disease with multiple recognized pathologies. Moreover, the description is not as definite as this type of subject matter permits, notably where specific pathologies are recognized and differentially distinguished, for example cognitive function or dementia vs. plaque burden. Moreover, absolution of disease so as to eliminate risk and to be sufficient to cure are beyond scope. Even today contributing factors to Alzheimer's such as genetic predisposition continue to be found and no known cure is recognized.

Accordingly, measurement of these goals or aims as in the preamble appear to be an impossibility as well as of indeterminate variation in scope. The circular language does not serve to clarify the scope of the claim where no testable endpoint is distinguished.

(10) Response to Argument

Double Patenting

Appellants assert that if the present claims are allowed in thier current form, Appellant is prepared to file a terminal disclaimer.

In response, the matter of patentability of instant claims in their current form has been forwarded to the Board for review and action.

Claim Rejections - 35 USC § 112, 1st Paragraph

Appellants arguements are presented within the Brief as extensively set forth at pp. 5-16 and will not be further reiterated herein, but are responded to as set forth below.

The, Examiner clarifies the primary issues with respect to enablement as follows. The rejection of record is one of scope. As the claims now stand before the Board, there are three main points of scope determined to extend beyond that enabled by the specification. The first is directed to the preamble recitations of "treating" and "prophylaxis", the second regards the language "an effective dosage to treat the disease" and "an effective dosage to effect prophylaxis" and the third regards the scope of peptides encompassed, now being those directed to "N-terminal segment of Abeta (SEQ ID NO:42) consisting of residues begining at residue 1 of Abeta and ending at residues 7-11 of Abeta."

Appellants arguments in response to the rejections of record make clear that the scope of the terms "treating" and "prophylaxis" should be read as set forth in the specification at pp. 36 lines 14-30. In this light, the specification makes clear that the scope of "prophylaxis" is inclusive to "an amount sufficient to eliminate (or reduce) risk, and "treating" is inclusive of "an amount sufficient to cure" amongst others. This scope is beyond that enabled by the specification because the specification does not achieve complete elimination or reduction of risk to the genetically predisposed animal and further fails to "cure" them as the animals in every treatment still produce beta amyloid plaque overproduction in brain. Accordingly, these recitations are deemed to be beyond the scope of that provided for by the specification. Indeed, even today there is no recognition of any cure or complete elimination of risk for Alzheimer's disease and the specification only provides for the measurement of inhibited or reduced plaque formations.

With respect to the "effective dosages" encompassed the aforementioned paragraph summarizes the scope to be provided and the scope to which the artisan must be able to measure so as to ascertain when the method has been sufficiently or effectively practiced. While the artisan has a measurement as provided for in the specification for inhibited or reduced plaque formation, no measurement is provided for the assessment of "eliminated risk" or "cure". Accordingly, these assessments are beyond scope.

With respect to the Wands analysis, one must look to the scope of the peptides now encompassed that have working embodiments within the specification. While the

specification provides experimentation with several peptide constructs, the important question with respect to the claims is how many embodiments provided are within the scope of the peptides encompassed by the claims. In this respect, there is only a single peptide construct that lies squarely within the scope of the peptides now encompassed and that is the Abeta1-7 peptide construct in tetrameric MAP formation as exemplified at pp. 99-100. While Abeta 1-5 and full length peptides are analyzed which provide for positive results, neither of these are within the scope of the genus claimed.

Accordingly, the assessment that only a single working embodiment within the scope of the genus claimed is a fair analysis. It is also highlighted that while the 1-5 and 1-7 construct provide for plaque reductions, an Abeta 1-12 construct was **not** effective. While there might be a basis given two members within the smaller genus of Abeta 1-5 to 1-7, there is no basis and not even a single working embodiment/example for the genus encompassing 1-8 to 1-11 that are within the scope claimed. The scope claimed of 1-7 to 1-11 has only a single species and therefore does not provide guidance to the extent of any wider scope. The art is evidenced to be unpredictable with respect to the fragments that work and those that do not, and there is no evidence of enablement with peptides in the range of 1-8 to 1-11. In contrast to support for enablement, the ineffectiveness of Abeta 1-12 argues against enablement for the broader range.

Appellants offer that in addition to peptide constructs, further support of enablement of peptides in the range of 1-11 is provided via data that most antibodies to full-length beta amyloid in monkeys map to within Abeta1-11. Here Appellants refer to

the teachings within Experiment XVII. However, this measurement is just of the stimulation of an antibody response, not for phagocytosis or clearing response that is belived to be the basis for the reduced plaque formation. Importantly Table 1-16 which analyzes for clearance activity does not appear to support epitopes from 1-8 to 1-11. A review of the epitopes that provide for both staining and phagocytosis within Table 16 indicates positive results only with full length and with epitopes within Abeta 1-7. Not a single antibody with epitope specificity extending to residues 1-8 to 1-11 are noted to be effective for both staining and phagocytic activity. Importantly antibody 6E10 (epitope 5-10 and 14A8(epitope 4-10) show no activity for phagocytosis even though the antibodies bind and stain. This evidences that binding of antibody is not necessarily the important event, but that clearing or phagocytic activity is and that the activities are separable. Accordingly evidence of antibodies binding to epitopes within 1-11 of monkeys, does not support that these epitopes provide for the activities of phagocytosis and clearance. An immune response may be generated over all portions of the peptide, but it does not clarify those portions that provide for protective immunotherapy absent evidence of such. In particular it is highlighted that not all antibodies with epitopes in this range are evidenced to reduce plaque formations upon long term administration.

Further, while Koller evidences possible reduction in cognitive decline with full-length peptide treatment, this construct is not within the scope of the peptides claimed, nor is there evidence of cognitive decline co-incident with plaque reduction using the claimed fragments, nor are the claims directed functionally to the measurement of cognitive decline. In contrast to Appellants assertion that "the claimed invention

requires only a single step of administering a peptide to a patient", all administrations that were deemed to be effective for any reduction in plaque formation required repeated administration over significant periods of time, and further no other indicator other than reduction in plaque formation was provided. If this assertion by Appellants were deemed to be the case, it would appear that the claims actually would then read on administration of any such fragment merely for the purpose of generating an immune or antibody response and that the generation of the immunospecific antibodies themselves would serve as prior art. However, this is not believed to be a fair reading of the claims.

The Examiner does not dispute that the instant animal model is an art accepted animal model of Alzheimer's disease and that the experimentation in such model is useful for research purposes. Nor does the Examiner suggest that human clinical trial data (with reference to Brana) is required. However, for the reasons aforementioned, the scope of enablement provided by the specification and/or within the Koller declaration is not deemed to be commensurate in scope with the claims, particularly as extended to elimination of risk or cure and to experimentation with peptide constructs not exemplified in scope to Abeta 1-8 to 1-11, particularly when Abeta 1-12 is evidenced to be ineffective.

In regards to the neurotoxicity events noted in Munch and the mechanistic comments with respect to Nichol, the Examiner does not believe that either are particularly on point to evidence treatment or prophylaxis as claimed with the claimed peptides. Again, the Examiner does not significantly rely on or require that Appellants

submit clinical data in humans. More relevantly, the aforementioned, in addition to Check are merely relevant with respect to the issue as to whether or not the model is recognized as commensurate with elimination of risk or cure, and on this point none of the references appear to evidence that the model system is efficacious at predicting elimination of risk or cure, particularly with the scope of peptides claimed in humans and accordingly do not offer evidence to support enablement in scope with the claims.

Appellants assert that "prophylaxis" is not of the same requirement as "prevention" but yet p. 36, lines 14-19 include "elimination or reduce the risk" and inclusive of "complications and intermediate pathological phenotypes presented during development of disease." Given this reading, the Examiner sees no distinction on any basis that "prophylaxis" has any less of a requirement than that of "prevention." To eliminate all risk and any type of pathological development appears commensurate with both prevention and cure.

With respect to Coliani and the terminology "effective dosage", the Examiner does acknowledge guidance as to both dosages and the length of time with respect to repeated dosages to produce effects such as reduced plaque formations/burden. However, this measurement is not in scope with the requirements of "treatment" and "prophylaxis" where both terms are inclusive of a "cure" or "elimination of risk", where such is not evidenced to be suitably measurable, where no regime provides for such and where no peptides other that Abeta 1-7 in tetrameric MAP formation are shown to be effective, and only then for a reduction in plaque formation. In contrast to the technology of screening monoclonals that has been widely used, the instant model

system of screening is new, evidenced to be unpredictable and is not recognized as commensurate within the scope of elimination of risk or cure in animals or humans. The claims provide no end-point of measurement with respect to either treatment and/or prophylaxis and an entire host of related measures may or may not be appropriate where the end-point is not specified. For example, there is no definitive guidance for completion of the claimed method where there is evidence for multiple measures such as the contemplation of a mere stimulation of an immune response, activation of B-cells, reduction in plaque morphology, reduced cognitive decline, change is histologic or behavioral symptoms of disease or any other amongst the host of related risks, symptoms or effects of disease. The importance missing is which of the measures actually correlates to a beneficial result. While a reduction in plaque formation might be viewed as being beneficial, other such measures do not appear to be reasonably correlated to the pathological manifestations associated with Alzheimer's disease.

While it is true that the art recognizes the major pathology associated with Alzheimer's as the occurrence of beta amyloid plaques, and that such may also be associated with reduced cognitive decline, such does not appear commensurate with evidence of enablement consistent with elimination of risk or cure. It is true that there is evidence for Abeta 1-5 (outside the scope of the claims) and Abeta 1-7 to provide for reduced plaque deposition in brains upon prolonged treatment. However, such does not establish evidence with respect to peptides Abeta 1-8 to 1-11, particularly where 1-12 is evidenced to be ineffective. A capacity of antibody administration to epitopes within 1-5, 3-6 and 3-7 further does not evidence or support enablement with respect to

peptide administration with Abeta 1-8 to 1-11. Nor does it appear that the mapping of the antibody response following immunization with full length beta amyloid evidences that peptide administration of Abeta 1-8 to 1-11 would be suitably effective for "treatment", "prophylaxis" or reduction in plaque formation. It is true that a methodology to screen may be present, yet the screen is not in scope with "treatment" or "prophylaxis" as defined in the specification nor have a sufficient number of species in scope with the genus claimed been tested for efficacy. Indeed only a single member is evidenced to be effective and even that single member is only to the extent of reduced plaque formation following a period of prolonged and repeated administrations.

Accordingly and collectively, the evidence of enablement is not commensurate in scope with that claimed.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Appellant's arguments are presented within the Brief as extensively set forth at pp. 17-18 and will not be further reiterated herein, but are responded to as set forth below.

Appellants make clear that the scope of treating and prophylaxis is as elaborated at p. 36, lines 14-23. Yet such description provides for a multitude of measurements where none is expressly or explicitly provided for in the claim. Neither is the broadest nor the narrowest scope adequately specified, and no end-point capable of measurement is provided. Appellant's reference to *Shatterproof Glass Corp v. Libbey Owns Ford Co.,* and *United Carbon Co. v. Binney Co.*, do not serve to further clarify the metes and bounds of any suitable measurements where no such

measurements are provided. While broad is not indefinite as in *Miller,* the artisan may only test for that which is recognized. A measurement for elimination of risk or cure is not recognized in the art and therefore no suitable measurement thereof is provided. The selection of end-point is also circular and indefinite to scope where any number of measurements may be applied. In instant case, cognition, reduction in plaque formation, immune activation, B or T cell responses all appear to be encompassed, yet the output or standard of ascertaining completion is not definitively specified. While other patents may contain such language, each patent is decided on its own merits. Here the "effective dosage" language is not exact where any number of known assays may or may not be applied and further where the scope of the circular terms with respect to treatment and prophylaxis bear no known methods of mesurement. Determining the endpoints within the scope of that claimed such as the elimination of risk or cure is beyond the skill recognized in the art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

SHARON TURNER, PH.D.
PRIMARY EXAMINER
1-20-06

Sharon L. Turner
Primary Examiner, Art Unit 1649

Conferees:

Brenda Brumback
SPE Art Unit 1647

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Janet Andres
SPE Art Unit 1648
1649

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER